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Pradman Qasba

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EDWARDS ANGELL PALMER & DODGE LLP

P.O. BOX 55874

BOSTON, MA 02205

EXAMINER

HUYNH, PHUONG N

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/580,108	Applicant(s) QASBA ET AL.	
	Examiner PHUONG HUYNH	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,43-45 and 49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,43-45 and 49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 6, 2009 has been entered.
2. Claims 1-3, 43-45 and 49 are pending and being acted upon in this Office Action.
3. Claim 2 is objected to because of duplicate "diuretic" and "muscle relaxant". Further, "hypnoticsleukotriene inhibitor" should have been "hypnotics, leukotriene inhibitor". "hypnotic: agent" should have been "hypnotic agent".
4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1-3, 43-45 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a targeted glycoconjugate comprising a specific bioactive agent as shown the specific anticancer agent listed at pages 14-15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase for delivery of biological agent to cancer cell, **does not** reasonably provide enablement for (1) any targeted glycoconjugate comprising any and all

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bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring as a pharmaceutical composition for use in medical therapy of any and all diseases such as treating and/or prevention of AID, (2) any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring wherein the bioactive agent is any "polypeptide", any "releasing factor", any "releasing factor inhibitor", any "carbohydrate", any "nucleic acid", any "vaccine", any "receptor agonist", any "receptor antagonist", any cough and cold preparation, any anti-antibiotic; any antiviral agent; any anti-fungal agent; any analgesics anesthetic; any anti-helminthic; anti-arthritis agent; any anti-asthmatic agent; any anticonvulsant; any antidepressant; any anti-diabetic agent; any anti-diarrhea; any anticonvulsant; any antihistamine; any anti-inflammatory agent; any toxin, any anti-migraine preparation; any anti-nauseant; any anticancer agent; any anti-parkinsonism drug; any anti-psychotic; any antipyretic; any anti-spasmodic; any anti-cholinergic; any sympathomimetic; any xanthine derivative; any cardiovascular agent; any anti-arrhythmic; any anti-hyperlipidemic agent; any anti-hypertensive; any diuretic; any anti-diuretic; any vasodilator; any central nervous system stimulant; any vasoconstrictor; any enzyme inhibitor; any hormone; any hypnotic agent, any muscle relaxant; any parasympatholytic; any central nervous system stimulant, any hypnotics any leukotriene inhibitor; any mitotic inhibitor; any genetic material; any psycho stimulant; any sedative; any anabolic agent; any vitamin; any herbal remedy; any anti-metabolic agent, any anxiolytic; any attention deficit disorder (ADD) drug; any attention deficit hyperactivity disorder (ADHD) drug; any neuroleptic agent; or any tranquilizer without the targeting compound in the claimed glycoconjugate for use in medial therapy of any and all diseases as set forth in claim 2, (3) any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring wherein the targeting compound comprises any glycoprotein, any glycolipid, or any carbohydrate as set forth in claim 3 for use in medial therapy of any and all diseases such as treating and/or prevention of AID, (4) any pharmaceutical composition comprising any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting

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compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and a pharmaceutical acceptable carrier as set forth in claim 43 for use in medical therapy of any and all diseases such as treating and/or prevention of AID, (5) any a kit comprising any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and instructions for use in any therapeutic or diagnostic method as set forth in claim 44 and (6) any targeted glycoconjugate comprising any and all bioactive agent and a targeting compound such as any antibody wherein the bioactive agent and the antibody are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring as set forth in claim 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass innumerable targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified UDP galactose acetyl group having a ketone attached to the C2 position of the galactose ring for use in any and all medical therapy.

Enablement is not commensurate in scope with how to use any unspecified targeted glycoconjugate comprising any bioactive agent and any targeting compound for the claimed targeted glycoconjugate.

The specification discloses only labeling of CREB or bovine lens α -crystallin using recombinant O-GlcNAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase, see pages 45-46. The specification discloses only modified UDP galactose—

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Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using mutant Y289L galactose transferase, see page 48 of the specification and summary of the specification.

The specification suggests the use of glycoconjugate for delivery of bioactive agent such as chemotherapeutic agent, toxin, alkylating agent, anti-proliferative agent, tubulin binding agents, mitomysins, bleomycins, diynes, paclitaxel, doxorubicin, camptothecin aminocamptothecin, 9-nitrocamptothecin, 10-hydroxy-camptothecin, irinotecan, adriamycin, daunorubicin, methotrexate, methoprine, dichloromethotrexate, mitomycin C, porfirimycin, 5-fluorouracil, 6-mercaptopurine, aminopterin, cytosine arabinoside, caminomycin, topotecan, 2'-O-glucopyranosyl camptothecin, taxanes (baccatins, cephalomannine, carboplatin, cisplatin, interferon-2A, interferon-2B, interferon-N3, 6-azauridine, aelaeinomyacin(s), aneitinabine, azacitidine, ... etoposide or etoposide phosphate, melphalan, leucosidine, vindesine, leucosine, vinorelbine, vincristine and vinblastine or diagnostic agent to relevant cancer cells or tissue using monoclonal and polyclonal anti-CD20 antibody, anti-IL-2Ra antibody, anti-B-FN antibody and binding fragments thereof, Type I interferon, Type II interferon, cytokines (e.g., interleukin-1 "IL-1", interleukin-2 ("IL-2"), interleukin-3 ("IL-3"), interleukin-4 ("IL-4"), interleukin-5, interleukin-6, Interleukin-7, interleukin-8 ("IL-8"), Interleukin- 10 ("IL- 10"), Interleukin- 11 ("IL- 11"), interleukin- 12 ("IL- 12"), interleukin- 13 ("IL- 13") and tumor necrosis factor ("TNF(α)"), epidermal growth factor (EGF), transforming growth factor- β , vascular epithelial growth factor ("VEGF"), transforming growth factor-alpha ("TGF α "), folate, vitamin-B12, vitamin B6, niacin, nicotinamide, vitamin A, ferritin and vitamin D, steroids, hormones, cofactors, cyclosporin-A, prostaglandin and prostacyclin.

Other than the specific glycoconjugate comprising the specific bioactive agent mentioned above and the specific targeting compound mentioned above wherein the chemotherapeutic agent and the antibody are joined by a modified UDP galactose acetyl group comprising a ketone group attached to the C2 position of the galactose ring using modified enzyme Y289L O-GlcNAc glycosyltransferase for delivery of the glycoconjugate to tumor cells, the specification does not teach the use of targeted glycoconjugate comprising any bioactive agent linked to any targeting compound via modified UDP galactose acetyl group comprises a ketone group attached to the C2 position of the galactose ring for treating any disease, much less for preventing all diseases.

Given the definition of targeting compound, there is insufficient guidance as to the binding specificity of such targeting compound in the claimed targeted glycoconjugate.

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Given the definition of "bioactive agent", there is insufficient guidance as to the structure associated with function of such bioactive agent, in turn, effective to treat which disease. Given the unlimited number of bioactive agent in the claimed glycoconjugate, there is a lack of in vivo working examples to show any unspecified glycoconjugate is effective to treat all disease, let alone to prevent any infectious disease such as AIDS, cancer.

With respect to claims 44 and 45, the intended use of the claimed the unspecified glycoconjugate is for any and all therapeutic or diagnostic methods (claims 44 and 45).

As stated in the MPEP, when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use), see MPEP 2164.01(c).

Further, the specification defines the term "treat" or "treating" includes treating, *preventing*, ameliorating, or inhibiting a disease, disorder and/or a symptom of a disease and/or a disorder of an organism, see page 5, lines 1-3.

The specification defines the term "bioactive agent" means any chemical or biological material or compound suitable for delivery that induces a desired effect in or on an organism, such as a biological or pharmacological effect, which may include, but is *not limited to*, (1) having a *prophylactic effect* on the organism and preventing an undesired biological effect such as preventing an infection, (2) alleviating a condition caused by a disease or disorder, for example, alleviating pain or inflammation caused as a result of the disease or disorder, and/or (3) either alleviating, reducing, or completely eliminating the disease or disorder from the organism. As used herein, "bioactive agent" also refers to a substance which may be used in connection with an application that is therapeutic or diagnostic in nature, such as in methods for diagnosing the presence or absence of a disease or disorder in a patient and/or in methods for the treatment or *prevention* of a disease or disorder in a patient. As used herein, "bioactive agent" refers also to substances which are capable of exerting a biological effect in vitro and/or in vivo. Examples of suitable bioactive agents include diagnostic agents, pharmaceuticals, drugs, synthetic organic molecules, proteins, peptides, vitamins, steroids and genetic material, including nucleosides, nucleotides and polynucleotides.

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The specification defines the term "pharmaceutical" or "drug" refers to any therapeutic or *prophylactic* bioactive agent which may be used in the treatment (including the prevention, diagnosis, alleviation, or cure) of a malady, affliction disease, disorder or injury in a patient. Therapeutically useful peptide, polypeptides and polynucleotides may be included within the meaning of the term pharmaceutical or drug.

In this case, the specification provided little or no guidance as to the binding specificity of the targeting compound beyond the mere mentioned of a laundry list of targeting molecules, covalently linked to a list of bioactive agent using a genetically engineered modified galactosyltransferase Y289L to append a ketone group at the carbon 2 of the UPD-GalNac.

The specification merely asserts that the claimed treat numerous diseases including preventing AIDS, see page 30 of specification. There is no guidance as to the binding specificity of the targeting compound for the claimed glycoconjugates. Given the numerous unspecified glycoconjugates, there is a lack of *in vivo* working example of such glycoconjugate could treat which out of many diseases, much less prevention of all diseases in a therapeutic method or medical therapy.

With respect to claim 44, pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Even if the targeting compound is an antibody (claim 49), there is insufficient guidance as to the binding specificity of such antibody joined to any and all unspecified bioactive agent.

The specification does not adequately teach how to effectively treat any diseases or diagnosing any diseases using any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide without guidance as to the binding specificity of such glycoconjugate to the development of effective *in vivo* human therapeutic compositions, commensurate in scope

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with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the conjugate exemplified in the specification or the breadth of glycoconjugate for treating any diseases, encompassed by the claims.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In *re wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Note, amending the claims to recite a glycoconjugate comprising a specific bioactive agent as shown the specific anticancer agent listed at pages 14-15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase would obviate this rejection. One of ordinary skill in the art would be able to make and use the specific targeted glyconjugate for delivery or targeting biological agent to cancer cell.

Applicants' arguments filed March 12, 2009 have been fully considered but are not found persuasive.

Applicants' position is that the instant claims are directed to a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) and wherein the UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Galactose is a well known saccharide to any person skilled in the art. The Specification teaches that the C2 position is favorable over other positions on the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C2 positions. For example, at page 48 of the specification, Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that C2 ketone

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functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 positions, including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ian et al., 2001; Wong et al., 1995) (and)... 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3-, 4, and 6-deoxy-Gal were transferred at reduced rates." (page 48).

In response, the claims are not drawn to a method making targeted glycoconjugate from their individual components such as bioactive agent and targeting compound joined by a modified saccharide compound which comprises galactose and reactive functional group attached to the C2 position of the galactose ring.

Amended claim 1 still recites a targeted glycoconjugate comprising any bioactive agent and any targeting compound, such as any glycoprotein, any glycolipid, any carbohydrate, or any antibody, wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group, and wherein the modified UDP-GalNAc comprises a reactive functional group attached to the C2 position of the galactose ring.

Enablement is not commensurate in scope with *how to use* any unspecified targeted glycoconjugate comprising any bioactive agent and any targeting compound mentioned above for treatment that encompassed prevention of any and all diseases, including AIDS.

The specification discloses only labeling of CREB or bovine lens α -crystallin using recombinant O-GlcNAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase, see pages 45-46. The specification discloses only modified UDP galactose--Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring because the mutant Y289L galactose transferase has been shown to tolerate unnatural substrates containing minor substitution at the C-2 position, including 2-deoxy, 2-amino, and 2-Acetyl substituents, see page 48 of the specification and summary of the specification.

The intended use of the claimed the unspecified glycoconjugate is for any and all therapeutic or diagnostic method (claims 44-45).

As stated in the MPEP, when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of

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being expressed in any cyanobacterium and thus defining the claimed gene by its use), see MPEP 2164.01(c).

In this case, the specification provided little or no guidance as to the binding specificity of the targeting compound beyond the mere mentioned of a laundry list of targeting molecules, bioactive agents joined by a list of modified saccharide compounds. The specification merely asserts that the claimed treat numerous diseases including AIDS, see page 30 of specification. There is no specific guidance as to the binding specificity of the targeting compound for the claimed glycoconjugates. Given the numerous unspecified glycoconjugates, there is a lack of *in vivo* working example of such glycoconjugate could treat any diseases such as AIDS. As such, it is unpredictable which disease(s) could be treated by the claimed unspecified glycoconjugate.

Further, pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat. App. & Inter. 1992).

The specification does not adequately teach how to effectively use any targeting glycoconjugate for treating and/or preventing any diseases or diagnosing any diseases without guidance as to the binding specificity of the targeting moiety and the structure associated with function of the bioactive agent in the claimed glycoconjugate to the development of effective *in vivo* human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of which unspecific glycoconjugate exemplified in the specification or the breadth of glycoconjugate for treating and preventing any diseases as encompassed by the claims.

7. Claims 1-3, 43-45 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

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skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1 and 45 are broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring as a pharmaceutical composition for use in medial therapy of any and all diseases, any disease such as AIDS.

Claim 2 is broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring wherein the bioactive agent is any polypeptide, any releasing factor, any releasing factor inhibitor, any carbohydrate, any nucleic acid, any vaccine, any receptor agonist, any receptor antagonist, any cough and cold preparation, any anti-antibiotic; any antiviral agent; any anti-fungal agent; any analgesics anesthetic; any anti-helminthic; anti-arthritis agent; any anti-asthmatic agent; any anticonvulsant; any antidepressant; any anti-diabetic agent; any anti-diarrheal; any anticonvulsant; any antihistamine; any anti-inflammatory agent; any toxin, any anti-migraine preparation; any anti-nauseant; any anticancer agent; any anti-parkinsonism drug; any anti-psychotic; any antipyretic; any anti-spasmodic; any anti-cholinergic; any sympathomimetic; any xanthine derivative; any cardiovascular agent; any anti-arrhythmic; any anti-hyperlipidemic agent; any anti-hypertensive; any diuretic; any anti-diuretic; any vasodilator; any central nervous system stimulant; any vasoconstrictor; any enzyme inhibitor; any hormone; any hypnotic agent, any muscle relaxant; any parasympatholytic; any central nervous system stimulant, any hypnotics any leukotriene inhibitor; any mitotic inhibitor; any genetic material; any psychostimulant; any sedative; any anabolic agent; any vitamin; any herbal remedy; any anti-metabolic agent, any anxiolytic; any attention deficit disorder (ADD) drug; any attention deficit hyperactivity disorder (ADHD) drug; any neuroleptic agent; or any tranquilizer for use in medial therapy of any and all diseases.

Claim 3 is broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound such as any glycoprotein, any glycolipid, or any carbohydrate wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring.

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Claim 43 is broadly drawn to a pharmaceutical composition comprising any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and a pharmaceutical acceptable carrier as a pharmaceutical composition *for use in medical therapy* of any and all diseases such as treating and/or prevention of AID.

Claim 44 is broadly drawn to a kit comprising any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and instructions *for use in any therapeutic or diagnostic method*.

Claim 49 is broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and a targeting compound such as any antibody wherein the bioactive agent and the antibody are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring.

The scope of the each genus of targeting compound and bioactive agent includes many members with widely differing structural, chemical, and physiochemical properties of targeting compound and bioactive agent such as widely differing amino acid sequences, nucleotide sequences, and biological functions in the claimed glycoconjugate. Furthermore, each genus is highly variable because a significant number of structural and biological differences between genus members exist.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry,

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whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF’s were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification does not reasonably provide a **written description** for (1) the *binding specificity* of the targeting compound such as any glycoprotein, any glycolipid, any carbohydrate or any antibody in the claimed glycoconjugate and (2) the structure associated with function of any bioactive agent, any bioactive agent such as polypeptide, any releasing factor, any releasing factor inhibitor, any carbohydrate, any nucleic acid, and any vaccine for use in any medical therapy that encompassed prevention of all diseases.

At the time of filing, The specification discloses only labeling of CREB or bovine lens α -crystallin using recombinant O-GlcNAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase, see pages 45-46. The specification discloses only modified UDP galactose—Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using mutant Y289L galactose transferase, see page 48 of the specification and summary of the specification.

The specification suggests the use of glycoconjugate for delivery of bioactive agent such as chemotherapeutic agent, toxin, alkylating agent, anti-proliferative agent, tubulin binding agents, mitomycins, bleomycins, diynes, paclitaxel, docetaxel, camptothecin aminocamptothecin, 9-nitrocamptothecin, 10-hydroxy-camptothecin, irinotecan, adriamycin, daunorubicin, methotrexate, methopterin, dichloromethotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, aminopterin, cytosine arabinoside, caminomycin, topotecan, 20-O-glucopyranosyl camptothecin, taxanes (baccatins, cephalomannine, carboplatin, cisplatin, interferon-2A, interferon-2B, interferon-N3, aelaeinomyacin(s), aneitabine, azacitadine, ... vindesine, leurosine, vinorelbine, vincristine and vinblastine or diagnostic agent to relevant cancer cells or tissue using monoclonal and polyclonal anti-CD20 antibody, anti-IL-2Ra antibody, anti-B-FN antibody and binding fragments thereof, Type I interferon, Type II interferon, cytokines (e.g., interleukine-1 “IL-1”, interleukin-2 (“IL-2”), interleukin-3 (“IL-3”), interleukin-4 (“IL-4”), interleukin-5, interleukin-6, Interleukin-7, interleukin-8 (“IL-8”), Interleukin- 10 (“IL- 10”), Interleukin- 11 (“IL- 11”), interleukin- 12 (“II,- 12”), interleukin- 13 (“II,- 13”) and tumor necrosis factor (“TNF(α)”), epidermal growth factor (EGF),

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transforming growth factor- β , vascular epithelial growth factor ("VEGF"), transforming growth factor-alpha ("TGF α "), folate, vitamin-B12, vitamin B6, niacin, nicotinamide, vitamin A, ferritin and vitamin D, steroids, hormones, cofactors, cyclosporin-A, prostaglandin and prostacyclin.

At the time of filing, applicants are not in possession of a genus of targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) that comprises a ketone attached to the C2 position of the galactose ring as a pharmaceutical composition for use in any medical therapy that encompassed prevention of any and all disease or any diagnostic method.

The specification provided little or no guidance as to the *binding specificity* of the targeting compound beyond the mere mentioned of a laundry list of targeting molecules. The term "glycoprotein", "glycolipid", "carbohydrate" or "antibody" does not enable one of ordinary skill in the art to envision the binding specificity of such targeting compound in the claimed glycoconjugate. Further, there is insufficient description as to the structure associated with function of any and all bioactive agents in the claimed glycoconjugate for use to treat and/or prevent any and all diseases, including AIDS, see page 30 of specification. There is no disclosure of any unspecified glycoconjugate could treat or prevent AIDS, for example.

The specification defines the term "treat" or "treating" includes treating, *preventing*, ameliorating, or inhibiting a disease, disorder and/or a symptom of a disease and/or a disorder of an organism, see page 5, lines 1-3.

The specification defines the term "bioactive agent" means any chemical or biological material or compound suitable for delivery that induces a desired effect in or on an organism, such as a biological or pharmacological effect, which may include, but is *not limited to*, (1) having a *prophylactic effect* on the organism and preventing an undesired biological effect such as preventing an infection, (2) alleviating a condition caused by a disease or disorder, for example, alleviating pain or inflammation caused as a result of the disease or disorder, and/or (3) either alleviating, reducing, or completely eliminating the disease or disorder from the organism. As used herein, "bioactive agent" also refers to a substance which may be used in connection with an application that is therapeutic or diagnostic in nature, such as in methods for diagnosing the presence or absence of a disease or disorder in a patient and/or in methods for the treatment or *prevention* of a disease or disorder in a patient. As used herein, "bioactive agent" refers also to

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substances which are capable of exerting a biological effect *in vitro* and/or *in vivo*. Examples of suitable bioactive agents include diagnostic agents, pharmaceuticals, drugs, synthetic organic molecules, proteins, peptides, vitamins, steroids and genetic material, including nucleosides, nucleotides and polynucleotides.

The specification defines the term "pharmaceutical" or "drug" refers to any therapeutic or *prophylactic* bioactive agent which may be used in the treatment (including the prevention, diagnosis, alleviation, or cure) of a malady, affliction disease, disorder or injury in a patient. Therapeutically useful peptide, polypeptides and polynucleotides may be included within the meaning of the term pharmaceutical or drug.

There is no disclosure of any *in vivo* working example that the claimed glycoconjugate could treat any disease such as AIDS, cancer, any autoimmune diseases, any bacterial infections, any psychiatric diseases, any cardiovascular diseases, etc, much less preventing all diseases from happening. In this case, the specification fails to disclose a representative number of species of each claimed genus, which includes many members with widely differing structural, chemical, and biological functions. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.).

With the exception of the specific modified galactose residue having a ketone group at C2 position of the galactose linked to a specific targeting agent and a specific bioactive agent using the specific recombinant mutant Y289L galactose transferase for targeting chemotherapeutic agent to cancer cells, or the specific glycoconjugate comprising the specific bioactive agent mentioned at page covalently joined to the specific antibody or cytokine for targeting the anti-cancer agent to tumor cell, the skilled artisan cannot envision the detailed chemical structure of the encompassed glycoconjugate and binding specificity of the targeting compound for treating, prevention, or diagnosing any and all diseases. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of

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the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

Because the described labeling of CREB or bovine lens α -crystallin involving modified galactose residue having a ketone group at C2 position of the galactose made by using the specific recombinant mutant Y289L galactose transferase for detection assays is not representative of the entire claimed genus of targeted glycoconjugate comprising a genus of bioactive agent such as any polypeptide, any releasing factor, any releasing factor inhibitor, any carbohydrate any nucleic acid linked to any targeting compound via modified UDP galactose acetyl group having a ketone functional group attached at the C2 position of the galactose ring for treating any diseases, one of skill in the art would conclude that applicant was not in possession of the claimed genus of targeted glycoconjugate. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1-3, 43 and 49 mentioned above.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 <http://www.USPTO.gov/web/menu/written.pdf>.

Note, amending the claims to recite a glycoconjugate comprising a specific bioactive agent as listed at pages 14-15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase would obviate this rejection.

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One of ordinary skill in the art would be able to envision the structure associated with function of the encompassed claimed glycoconjugate for delivery or targeting the specific biological agent to cancer cell.

Applicants' arguments filed November 6, 2009 have been fully considered but are not found persuasive.

Applicants' position is that as amended, the claims to particularly recite targeted glycoconjugate compounds comprising a bioactive agent and a targeting compound, wherein the bioactive agent and targeting compound are linked by a modified UDP galactose acetyl group (UDP-GalNAc) and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Targeted glycoconjugate compounds are described at page 8. Modified saccharide compounds are described at page 9. Targeting compounds are described at page 10, page 18. Bioactive agents are described beginning at page 10.

Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that "the ketone functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 position including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ian et al., 2001; Wong et al, 1995) (and)... 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3, 4 and 6 deoxy Gal were transferred at reduced rates." (page 48).

Applicants submit that the claims are sufficiently described in the specification to reasonably convey to one skilled in the relevant art that The inventor, at the time the application was filed, had possession of the claimed invention, Applicants respectfully request that the forgoing rejections be withdrawn.

In response, the rejected claims are still broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent, any bioactive agent such as any polypeptide, any carbohydrate, any nucleic acid, any vaccine, any receptor agonist or any receptor antagonist and any and all targeting compound such as any glycoprotein, any glycolipid, any carbohydrate or any antibody wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring as a pharmaceutical composition for use in *medical therapy* of any and all diseases such as treating and/or prevention of AIDS.

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The amended claims still lack the *binding specificity* of the targeting compound and the structure associated with function of bioactive agent for the claimed conjugates effective to treat or prevent any and all diseases.

The specification fails to disclose a representative number of species of glycoconjugate for claimed genus, which includes many members with widely differing structural, chemical, and biological functions. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Note, amending the claims to recite a glycoconjugate comprising a specific bioactive agent such as the specific anticancer agent listed at pages 14-15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase would obviate this rejection. One of ordinary skill in the art would be able to envision the structure associated with function of the encompassed claimed glycoconjugate for delivery or targeting the specific biological agent to cancer cell.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).
10. Claims 1-3 and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Vocadlo et al (newly cited, Proc Nat Acad Sci USA 100(16): 9116-9121, August 5, 2003; PTO 892).

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Vocadlo et al teach a glycoconjugate comprising a bioactive agent such as FLAG phosphine probe or biotin phosphine probe and a targeting compound such as recombinant nuclear pore protein p62 wherein the reference probe and nuclear pore protein 62 are joined by a modified UDP galactose acetyl group comprises a ketone group attached to the C2 position of the galactose ring (see page 9119, Figure 4B, in particular. The reference nuclear pore protein p62 is o-Glc-NAc glycosylated glycoprotein (see page 9119, right col., page 9120, right col., first paragraph, in particular). Claim 2 is included in this rejection the reference bioactive agent FLAG phosphine is a polypeptide (see caption of Fig 4, in particular). Claim 3 is included in this rejection because reference nuclear pore protein p62 is o-Glc-NAc glycosylated glycoprotein (see page 9119, right col., page 9120, right col., first paragraph, page 9120, paragraph bridging left and right columns, in particular). Claim 45 is included in this rejection because a product is a product, irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

11. Claims 1-3 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 7,332,355 (claimed priority to provisional application 60/523,523 filed November 18, 2003; PTO 892).

The '355 patent teaches a glycoconjugated comprising a bioactive agent such as radioactive substance such as I¹²⁵ or antibody binding probe (see entire document, col. 12, lines 3-10, in particular), and a targeting compound such as CreB protein or α -crystallin or peptide (see col. 17, lines 25-67, in particular) wherein the reference radioactive substance and CreB protein or α -crystallin are joined by a modified UDP galactose acetyl group comprising a ketone attached to the C2 position of the galactose ring (see entire document, col. 17, lines 11 through 39, Figure 1B, Figure 3, Figure 13, in particular) for diagnostic method. The reference o-GalNAc CREB protein is o-glycosylated glycoprotein (see col. 8, lines 36-63, col. 22, lines 59-61, in particular). Claim 45 is included in this rejection because a product is a product, irrespective of its intended use. Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:
- A person shall be entitled to a patent unless:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
14. Claims 1-3, 43-45 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 7,265,085 (of record, issued Sept 4, 2007; claimed priority to earliest provisional application 60/328,523 filed Oct 10, 2001; PTO 892) in view of US Pat No 7,332,355 (newly cited, claimed priority to provisional application 60/523,523 filed November 18, 2003; PTO 892), Ramakrishnan et al (of record, J Biol Chem 277(23): 20833-20839, June 2002; PTO 892) and/or Hang et al (of record, J Am Chem 123: 1242-1243, 2001; PTO 1449).

The '085 patent teaches various targeted glycoprotein such as transferrin-SA linker-GDNF wherein the reference targeting compound such as transferrin and bioactive agent such as GDNF are joined by a modified o-Glc-NAc modified galactose using β -1,4 galactosyl transferase (see col. 349-350, claims 1-4 of '085 patent, back ground of invention, in particular). The reference modified galactose or Gal to contain a ketone group (see paragraph 26, Background of invention, paragraphs 579-592, in particular). The '085 patent also teaches a pharmaceutical composition comprising the reference glycoconjugate and a pharmaceutical acceptable carrier such as PBS or saline (see paragraphs 1189-1193, in particular). The '085 patent also teaches a kit comprising the reference glycoconjugate and instructions for how to use such glycoconjugate (see paragraph 1450, in particular). The '085 patent further teaches glycopeptide molecule having a modified sugar molecule or other compound conjugated thereto confers a beneficial property on the peptide; the conjugate molecule is added to the peptide enzymatically because enzyme-based addition of conjugate molecules to peptides has the advantage of regioselectivity, stereoselectivity and having desired and or modified glycan structures that can be produce at an

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industrial scale for the efficient production of improved therapeutic peptides (see summary of invention).

The invention differs from the teachings of the reference only in that the glycoconjugate wherein the modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of galactose ring.

The '355 patent teaches a method of making glycoconjugate comprising a bioactive agent such as antibody binding probe (see entire document, col. 12, lines 3-10, in particular) and a targeting compound such as CREB protein or α -crystallin or peptide (see col. 17, lines 25-67, in particular) wherein the reference radioactive substance and CreB protein or α -crystallin are joined by a modified UDP galactose acetyl group comprising a ketone attached to the C2 position of the galactose ring (see entire document, col. 17, lines 11 through 39, Figure 1B, Figure 3, Figure 13, in particular) for diagnostic method. The '355 patent teaches the advantage of using engineered mutant to selectively transfer an unnatural ketone functional group onto O-GlcNAc glycosylated proteins where the ketone moiety serves as a versatile handle for the attachment of any protein of interest such as biotin, fluorescent reagent, enzymatic reagent, luminescent probe, protein-binding probe, antibody-based binding, radioactive probe, or enzyme (see abstract, col. 2, lines 12-26, in particular).

Ramakrishnan et al teach a modified β 1,4-galactosyltransferase (β 4Gal-T1) having a tyrosine at position 289 substitute for Lysine that enhances the GalNAc-transferase activity equal to that of Gal-T activity (see entire document, page 20837, col. 1, page 20836, col. 1, in particular). The reference modified enzyme creates the required optimal space between the keto group of C2 atom of galactose (Gal) and the side chain of Tyr-289 enzyme creating a site specific conjugation (see FIG 22A-C, in particular).

Hang et al teach the use of unnatural or modified monosaccharide such as 2-ketosugars or 2-keto isostere of GalNAc (galacto-N-Acetyl) sugar or 2-N-acetaminodugars as the substrate for GalNAc transferase for metabolic glycoprotein engineering in CHO cells; the 2-Keto GalNAc might be exploited to introduce unique chemical reactivity into secreted glycoproteins produced by large-scale recombinant expression of protein, allowing further selective modification (see page 1243, col. 2, last paragraph, in particular). Hang et al further teach the ketone reactive group produced by 2-ketosugars can be used as a molecular handle and more accessible for chemical reaction with biotin hydrazide (see page 1243, col. 1-2, in particular).

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to join/link any bioactive agent with any o-GlcNAc posttranslational modified protein or targeting compound of the '085 patent using modified UDP-GlcNAc that comprises a ketone functional group attached to the C2 position of the galactose ring as taught by the '355 patent, or Ramakrishnan et al or 2-ketosugars or 2-keto isostere of GalNAc (galacto-N-Acetyl) as a molecular handle as taught by Hang et al.

One having ordinary skill in the art would have been motivated with the expectation of success to join any bioactive agent and any targeting compound to form a glycoconjugate using modified UDP galactose acetyl group (UDP-GalNAc) comprising a ketone group attached to the C2 position of the galactose ring because the modified β 1,4-galactosyltransferase (β 4Gal-T1) having a tyrosine at position 289 substitute for Lysine is high selectivity enhances the GalNAc-transferase activity as taught by the '355 patent (see col. 9, line 37-43, col. 11, lines 1-3, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to join any bioactive agent and any targeting compound to form a glycoconjugate using modified UDP galactose acetyl group (UDP-GalNAc) comprising a ketone group attached to the C2 position of the galactose ring because the modified β 1,4-galactosyltransferase (β 4Gal-T1) enzyme enhances the GalNAc-transferase activity equal to that of unmodified Gal-T activity in addition to site specific recognition of the ketone group in the C2 position of the galactose as taught by Ramakrishnan et al (see entire document, page 20837, col. 1, page 20836, col. 1, in particular).

One having ordinary skill in the art would have been motivated to use 2-ketosugars or 2-keto isostere of GalNAc (galacto-N-Acetyl) sugar as the substrate for conjugation because Hang et al teach the 2-Keto GalNAc might be exploited to introduce unique chemical reactivity into secreted glycoproteins produced by large-scale recombinant expression, allowing further selective modification (see page 1243, col. 2, last paragraph, in particular).

One having ordinary skill in the art would have been motivated to do use 2-ketosugars or 2-keto isostere of GalNAc (galacto-N-Acetyl) sugar or 2-N-acetaminodugars as the substrate for conjugation because Hang et al teach the ketone group can be used as a molecular handle and more accessible for chemical reaction with biotin hydrazide (see page 1243, col. 1-2, in particular).

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One having ordinary skill in the art would have been motivated with the expectation of success to make and use site specific conjugation of glycoconjugate for drug delivery because the '085 patent teaches enzyme-based addition of conjugate molecules to peptides has the advantage of regioselectivity, stereoselectivity and can be produce at an industrial scale for the efficient production of improved therapeutic peptides (see summary of invention). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed November 6, 2009 have been fully considered but are not found persuasive. Applicants' position is that the '085 patent provides no teachings or suggestion that a modification at the C2 position of the saccharide ring is preferable over any position in the saccharide ring and it would not be obvious to one of ordinary skill in the art at the time the invention was made to substitute the linker substrate of O-linked SA modified galactose of the '085 patent for the 2-ketosugars or 2-ketoisostere of GalNAc as taught by Huang where the ketone bearing sugar can react with a number of nucleophiles.

In response, in addition to the conjugate as shown at col. 68, line 6, the '085 patent teaches other conjugates such as transferrin-SA linker-GDNF wherein the reference targeting compound such as transferrin and bioactive agent such as GDNF are joined by a modified o-GlcNAc modified galactose using β -1,4 galactosyl transferase (see col. 349-350, claims 1-4 of '085 patent, back ground of invention, in particular). The reference modified galactose or Gal to contain a ketone group (see paragraph 26, Background of invention, paragraphs 579-592, in particular).

The invention differs from the teachings of the reference only in that the glycoconjugate wherein the modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of galactose ring.

However, the '355 patent teaches glycoconjugate using modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of galactose ring to link any protein of interest such as biotin, flourescent reagent, enzymatic reagent, luminescent probe, protein-binding probe, antibody-based binding, radioactive probe, or enzyme onto the O-GalNAc glycosylated protein such as CREB, or α -crystallin or peptide (see col. 17, lines 25-67, in particular). The '355 patent teaches the method exploits the ability of an engineered mutant

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β 1,4-galactosyltransferase (β 4Gal-T1) having a tyrosine at position 289 substitute for Lysine that enhances the GalNAc-transferase activity equal to that of Gal-T activity (see abstract, in particular). The structure of the conjugate of '355 patent is the same as that of the claimed glycoconjugate, see Figure 1B of the patent and compared to the figure disclosed in the specification (see page 49 of instant specification).

Likewise, Ramakrishnan et al teach the use of modified β 1,4-galactosyltransferase (β 4Gal-T1) having a tyrosine at position 289 substitute for Lysine that enhances the GalNAc-transferase activity equal to that of Gal-T activity (see entire document, page 20837, col. 1, page 20836, col. 1, in particular). The reference modified enzyme creates the required optimal space between the keto group of C2 atom of galactose (Gal) and the side chain of Tyr-289 enzyme creating a site specific conjugation (see FIG 22A-C, in particular).

15. No claim is allowed.
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.
17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644

January 29, 2010